Egyptian Rheumatology and Rehabilitation

REVIEW

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Update on the utility of trabecular bone score (TBS) in clinical practice for the management of osteoporosis: a systematic review by the Egyptian Academy of Bone and Muscle Health

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Abstract

Trabecular bone score (TBS) is a grayscale textural assessment resulting from a computed evaluation of pixel gray-level variations in previously obtained lumbar spine DXA images. It is an index of bone microarchitecture correlated with parameters of bone strength. Higher values of TBS indicate a better microarchitecture, whereas lower values indicate a degraded microarchitecture. TBS can be used alongside Fracture Risk Assessment tool "FRAX" and bone mineral density (BMD) to enhance the assessment of fracture risk and to inform treatment initiation and monitoring. A systematic review was carried out aiming to update the evidence on the clinical use of the TBS in the management of both primary and secondary osteoporosis. Results revealed that in both primary and secondary osteoporosis, TBS enhances the prediction of fracture risk, and when adjust with BMD and clinical risk factors, it is able to inform the decision-making process regarding initiating osteoporosis therapy and the choice of anti-osteoporosis medication. Evidence also implies that TBS provides valuable adjunctive information in monitoring osteoporosis therapy. In conclusion, this work provides an up-to-date evidence-based review and recommendations which informs the utility of trabecular bone score in standard clinical practice.

Keywords Trabecular bone score, TBS, DXA, BMD, Bone mineral density, Osteoporosis, Sequential, Anti-osteoporosis therapy, Egyptian Academy of Bone Health

Background

Osteoporosis, by definition, entails two major bone changes; the first is the decrease in bone mass (bone quantity), and the second is the deterioration of trabecular microarchitecture (bone quality). Both lead to an increase in the incidence of bone fragility and consequently low impact bone fractures. Bone mass is measured by the dual-energy x-ray absorptiometry (DXA) which gives detailed information about the bone mineral density in three common body areas: the lumbar spine, the hip joint, and the distal forearm. Using DXA, osteoporosis is defined as a T score of − 2.5 or less. Unfortunately, fragility fracture was reported to occur in many

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patients with T score higher than − 2.5 which denotes the important influence of bone structural properties on bone strength [1].

The structural properties of bone include geometry and microarchitecture (trabecular number, thickness, connectivity, separation, and cortical thickness and porosity), whereas the material properties include bone mineral content (crystal size and orientation), collagen composition, and damage accumulation [2]. Several methods have been developed to measure the micro-architectural component of bones; these included histomorphometric or micro computed tomography (micro-CT) examination of the iliac crest bone biopsy which was highly informative but invasive and not widely available [3]. Other procedures include micro-magnetic resonance imaging (micro-MRI) and high-resolution peripheral quantitative computed tomography (HR-pQCT) which although non-invasive but overly expensive [4, 5].

This work was carried out to provide an up-to-date evidence-based review and recommendations which inform the utility of trabecular bone score (TBS) in standard clinical practice.

Methods

Design

The evidence-based review and recommendations which inform the utility of TBS in standard clinical practice were formulated based on the clinical evidence-based guidelines (CEG) development process protocol which involves a qualitative synthesis of statements and recommendations based on the existing scientific evidence and clinical experience. The manuscript conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews [6].

Development stages

Core team

It was formed of four experts with recognized experience in osteoporosis management. The criteria for their selection included professional knowledge and experience (at least 8 years of experience) in the field of osteoporosis, its management and practice in the Egyptian Health System, and active participation in scientific research on osteoporosis. The core team coordinated and supervised the teamwork, assisted with developing the scope of the project, and reached a consensus on the key questions to include in this update.

Key clinical questions

This update was centered on a series of structured key questions that define the targeted benefits and harms of interventions and formulating recommendations. The evidence to answer the clinical questions was collected according to the following steps: formulation of clinical questions, structuring of questions, search for evidence, critical evaluation and selection of evidence, presentation of results, and recommendations. These questions, shown in Table 1, formed the basis of the systematic literature search and consequently the clinical care standards. Supplement 1 demonstrates the levels of evidence.

Literature review team

Led by an experienced literature review consultant and based on the specific research questions identified to focus on TBS, the literature review was conducted with the assistance of an expert in methodology. To acquire proper evidence-based background knowledge for considerations, a systematic literature search was carried out using PubMed/ MEDLINE, Embase, and Cochrane databases. Following the data abstraction, reviewing the published recommendations, and the quality of evidence rating [7, 8], revision was carried out by the experts responsible for the literature review, who provided a comprehensive list of propositions for the use of TBS in clinical practice based on the available research evidence and their own clinical expertise. Duplicate screening of literature search results was performed electronically. Additional relevant studies were retrieved by reviewing the reference lists of studies identified with the database search strategies that met the inclusion criteria. The level of evidence was determined for each section using the Oxford Centre for Evidence-Based Medicine (CEBM) system [8].

Study selection

Relevant studies were selected by applying inclusion and exclusion criteria to the literature retrieved with the search strategies.

Inclusion criteria

Articles included were systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational

Table 1 Key clinical questions

1. Can TBS be used as a measure of bone quality?
2. What is the relation between TBS and BMD?
3. What is the best approach to integrate TBS in clinical practice?
4. What are the confounding factors that might affect TBS measurement?
5. What is the added value of considering TBS for the initiation and monitoring of osteoporosis therapy?
6. What is the role of TBS in fracture risk prediction in secondary osteoporosis?
7. What are the pros and cons of TBS?

studies including cohort, case control, and cross-sectional studies.

Exclusion criteria

Editorials, commentaries, conference abstracts and non-evidence-based narrative/personal reviews, and manuscripts lacking English version were excluded.

Critical appraisal (risk-of-bias assessment)

The Joanna Briggs Institute (JBI) tool for cross-sectional studies [9] was used to evaluate the quality of the studies. Outcomes of the critical appraisal were presented as answers (yes, no, unclear, or not applicable).

If up to seven items were fulfilled, this was considered as a low risk of bias, and the overall appraisal of the study was "include." In case there was inappropriateness of the sample or the identification of the condition did not use valid methods, the study was then considered as a high risk of bias, and it qualified "exclude." A study was considered as seeking further info if at least two items were unclear.

Results

Literature research and evidence selection

In the study selection process, 764 potentially relevant studies were identified by the search strategy. Five-hundred ninety-five were excluded: 14 duplicates and 581 by screening of title and abstracts (publication type, not TBS, and no fracture outcome). Therefore, 169 relevant studies were included for full article review. Sixty-three studies were excluded as they did not meet the inclusion criteria; consequently, 106 studies were included in this work: 55 studies investigated TBS and fracture prediction in primary and secondary osteoporosis, and 51 studies investigate TBS and treatment monitoring in both primary and secondary osteoporosis (Supplement 2).

Risk-of-bias assessment

Each study was assessed for the variable JBI tool domains, and a consensus was reached. Nice studies were considered as a high risk-of-bias study, hence excluded.

Statements and recommendations

Can TBS be used as a measure of bone quality?

The principal is as follows: TBS is a non-expensive, non-invasive indirect bone quality measurement used since 2008. It is a textural index that evaluates grayscale variations in pixels of the lumbar spine images obtained by DXA machines. As DXA image is retrievable even from many years, TBS can be applied on any new or old DXA image. Some studies have reported that TBS is correlated with some bone microarchitecture parameters such as trabecular number, thickness, and connectivity [10, 11]. The main principle of TBS is that areas containing dense trabeculae produce an image with high pixel values and of low amplitude, while porous areas with few thin trabeculae produce an image with low pixel values and of high amplitude. High TBS values indicate good architecture, while lower levels indicate trabecular degradation.

Recommended cut-offs in the literature are $TBS > 1.350$ as normal TBS between 1.200 and 1.350 as partially degraded microarchitecture and $TBS < 1.200$ as degraded microarchitecture [12]. However, because of different populations' characteristics, it is recommended to use local reference values, if possible, for each gender.

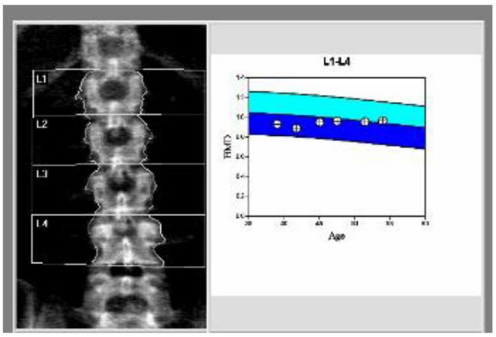
What is the relation between TBS and BMD? Level of evidence (LOE): 3-C

A BMD test assesses the amount of calcium and other minerals in bone and therefore is clearly one of the major determining factors of bone strength and fracture risk [13]. However, using BMD for the evaluation of fracture risk was reported to lack sensitivity. NORA study revealed that low trauma fractures occur in osteopenia subjects than in individuals with osteoporosis [1]. Consequently, it has been suggested that other parameters, together with BMD, account for the increased fracture risk. These include micro-architecture, bone geometry, and micro-damage, turnover, and mineralization [14, 15]. Considering microstructure, standard DXA measures do not provide any insight.

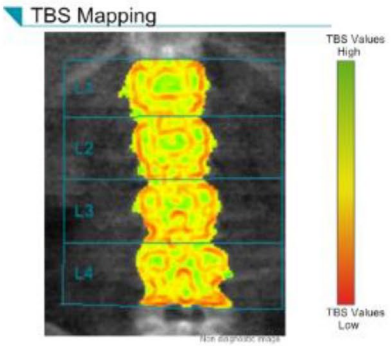
Since TBS, in comparison to BMD, provides a validated index of bone microarchitecture and correlates with mechanical properties of bone, the TBS has been dissociated from the BMD evaluation [16]. This would explain the finding of vertebrae with similar BMD measures may have different TBS values (Fig. 1). The trabecular condensation is presented in the form of chess board like figure where the lighter gray shade represents good trabecular structure, and the deeper gray shades represent the more degraded trabeculae.

TBS can help in diagnosing osteoporosis when the clinical suspicion is high but not confirmed by the BMD [17]. However, unlike BMD, TBS is insensitive to the vertebral degenerative artifacts and the presence of osteophytes. This would be an added value for the TBS to assess the lumbar vertebral bone quality [18, 19]. In the work carried out by Leslie and colleagues [20], they noted large variation in TBS values in between the lumbar vertebrae with an increase from upper to lower vertebrae, and that there is strong association between fracture risk prediction and TBS level of individual vertebrae. On the other hand, TBS was not recommended to be used by itself in monitoring patients with vertebral fracture risk factors [21]. At 2012, TBS was approved by the Food and Drug Administration (FDA) to be used as a fragility fracture

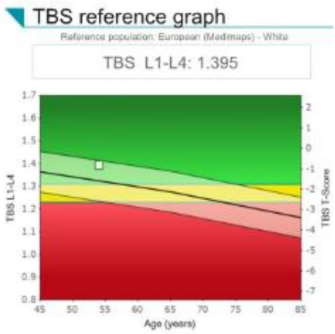
A



Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	12.35	11.70	0.947	-0.4	96	0.5	106
L2	13.04	12.24	0.939	-0.8	91	0.2	102
L3	13.16	11.91	0.905	-1.6	84	-0.6	93
L4	15.43	16.05	1.040	-0.2	98	0.9	110
Total	**53.98**	**51.90**	**0.961**	**-0.8**	**92**	**0.2**	**103**



Region	TBS	TBS T-Score	TBS Z-Score	BMD
L1	1.477	---	---	0.947
L2	1.429	---	---	0.939
L3	1.338	---	---	0.905
L4	1.336	---	---	1.040
L1-L4	1.395	-0.8	0.8	0.961
L1-L3	1.415	-0.8	1.3	0.930
L1-L2	1.453	-0.4	2.0	0.943
L2-L3	1.383	-1.4	0.4	0.922
L2-L4	1.368	-1.2	0.2	0.966
L3-L4	1.337	-1.3	-0.3	0.978



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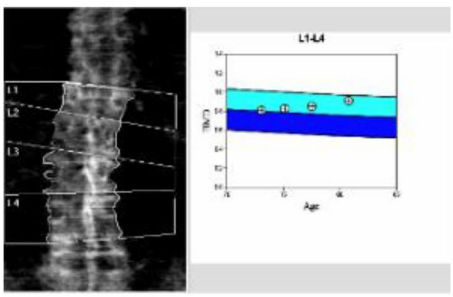
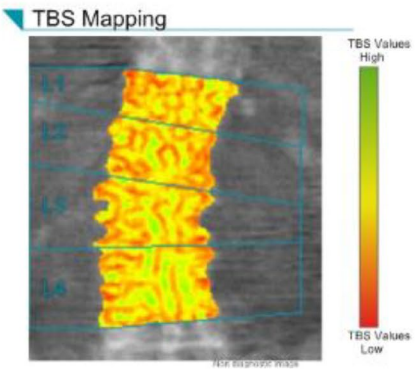


Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	9.92	9.04	0.911	-0.7	92	1.7	125
L2	11.74	9.68	0.824	-1.9	80	0.8	112
L3	12.88	12.04	0.935	-1.4	86	1.5	121
L4	16.18	15.30	0.946	-1.0	89	1.8	127
Total	**50.72**	**46.06**	**0.908**	**-1.3**	**87**	**1.5**	**121**



Additional results

Region	TBS	TBS T-Score	TBS Z-Score	BMD
L1	0.986	---	---	0.911
L2	0.981	---	---	0.824
L3	1.063	---	---	0.935
L4	1.186	---	---	0.946
L1-L4	1.054	-4.6	-1.5	0.908
L1-L3	1.010	-5.3	-1.5	0.891
L1-L2	0.983	-5.6	-1.4	0.864
L2-L3	1.022	-5.4	-2.0	0.882
L2-L4	1.077	-4.4	-1.5	0.907
L3-L4	1.124	-3.6	-1.3	0.941

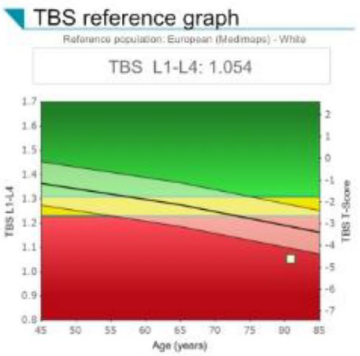


Fig. 1 TBS can help in diagnosing osteoporosis when the clinical suspicion is high but not confirmed by the BMD. **A** shows 67-year-old woman with normal BMD and TBS, whereas (**B**) shows 71-year-old woman DXA scan showing multiple compression fracture of the lumbar vertebrae and T score of – 1.3, while the TBS of the lumbar vertebrae was 1.054 denoting marked deteriorated bone microarchitecture

predictor complementary to BMD measuring. In concordance, the International Society for Clinical Densitometry, among over 30 national and international clinical guidelines, had recommended TBS as an important predictor of both hip and major osteoporotic fractures [22].

Discordance between BMD and TBS (for example, normal BMD and degraded TBS) should prompt consideration of further clinical evaluation for probable causes of secondary osteoporosis. Vertebral fracture assessment (VFA) should be considered for osteopenic patients with degraded TBS.

In contrast to BMD which is applicable on patients between 40 and 90 years old, TBS have been studied as an indicator of bone strength in premenopausal women. Heiniö et al. [23] have examined the association between TBS value and exercise performance in 88 athlete females at postpubertal and premenopausal age. They reported that athletes who were practicing high axial loads had higher TBS values compared to those who practiced moderate impact loading exercises, and these values were independent to the BMD measures at lumbar spines.

What is the best approach to integrate TBS in clinical practice?

One of the most important implications of TBS in standard clinical practice is the findings of an earlier study which reported its ability to predict fragility fracture in the general population independent of the FRAX score (Fig. 2) [24]. Furthermore, in postmenopausal females, several studies [25, 26] have demonstrated the efficacy of TBS score to predict fragility fracture of the hips and spine besides the major osteoporotic fractures (MOF) aside from the BMD value. On average, every 1-point standard deviation (SD) decline in the TBS leads to a 30–40% increase in the risk of fragility fractures in postmenopausal women. Whereas in men over 50 years old, TBS was found to predict MOF and hip fractures better than vertebral fractures [27] (LOE 1.B).

Recent TBS software versions (e.g., *TBS* 3.1.2) have been updated with new tools and facilities to integrate the TBS measure into the individual patient's assessment. Examples are TBS-adjusted FRAX® and TBS-adjusted BMD T score, which can guide in choosing the proper anti-osteoporotic medication. Automated conclusions based on medical society guidelines have also been added. Lastly, the combined BMD T score and TBS scores was reported to provide information about the bone resilience index. The "Bone Resilience Index" is an interpretive tool provided by the manufacturer, comprising combinations of categories of BMD (normal, osteopenic, or osteoporosis) and TBS (normal, partially degraded, or degraded).

TBS-adjusted FRAX is an algorithm that is derived from the WHO fracture assessment score to predict the 10-year probability of MOF and hip fractures by adding the TBS value to improve the accuracy of FRAX results [26–33]. Studies showed that TBS-adjusted FRAX® had elevated the accuracy level of calculated fracture probabilities in some populations [34–39]. On the other hand,

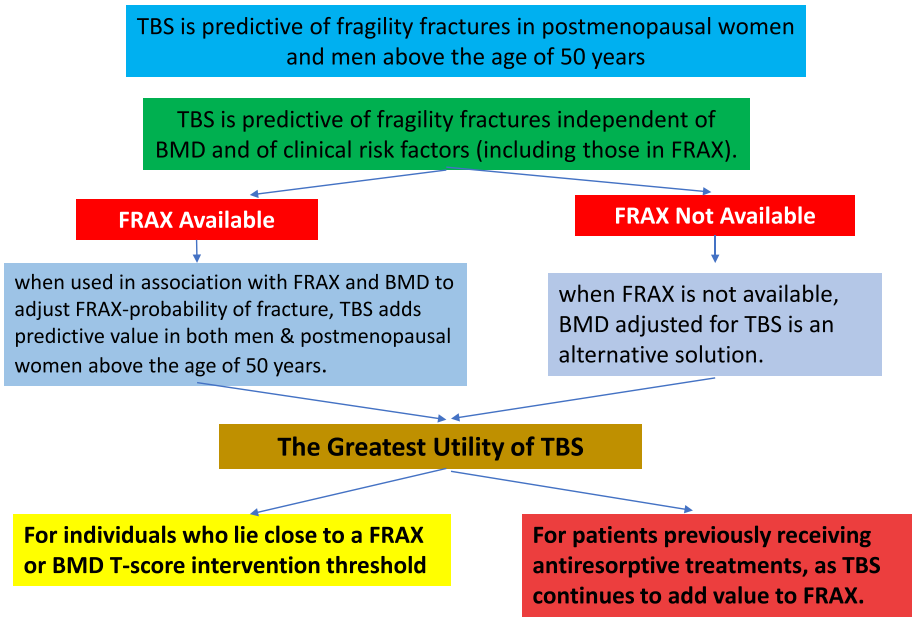


Fig. 2 Algorithm showing the use of TBS in fracture risk prediction in postmenopausal and male osteoporosis

other studies failed to prove the predictive superiority of the TBS-adjusted FRAX in some other populations [40–42] (LOE 3.B).

On another front, the adjustment of BMD T score for TBS has been considered a relevant clinical progress in the management of osteoporosis. In a large meta-analysis, TBS was found to be a validated independent predictive factor of osteoporotic fracture. However, though TBS was reported to significantly predict the incidence of fracture(s), independent of BMD (*HR* = 2.01, 95% *CI* 1.54, 2.63) [34], the combination of TBS with lumbar spine BMD or the lowest BMD significantly enhanced fracture prediction, for both major osteoporotic fractures and hip fracture compared to either of the tools alone. Figure 3 summarizes the value of integrating TBS in clinical practice as a predictive tool for fragility fractures (LOE 3.C).

What are the confounding factors that might affect TBS measurement?

Age is a considerable factor that affects the TBS value. In a cross-sectional study [43], the proportion of elderly persons eligible for treatment according to the FRAX cutoff values were nearly similar when FRAX and TBS-adjusted FRAX were compared. While using age stratification, the proportion of eligible persons were increased on using the TBS-adjusted FRAX than FRAX alone in the age groups (60–70) and (70–80) years old. In agreement with this, Simonelli and colleagues [44] reported significant decrease in lumbar TBS values with age, and the annual decline rate in TBS values increased after the age of 65 (LOE 3.B).

High body mass index and thick, soft tissue can cause underestimation of the TBS values; however, this limitation has been improved in recent software versions of the TBS [45]. In the study of Dufour and colleagues [46], age-related changes in TBS values were investigated in 5942 French ladies between 45 and 85 years old, and it was reported that TBS values inversely correlated to BMI and weight but not height (LOE 3.C).

Other reported clinical risk factors that could lead to reduced TBS included prior major fracture, recent glucocorticoid intake, rheumatoid arthritis, chronic obstructive pulmonary disease, and high alcohol intake. In contrary, recent antiosteoporosis treatment was associated with better TBS results [47].

What is the added value of considering TBS for the initiation and monitoring of osteoporosis therapy?

TBS and treatment decision-making As per international as well as national osteoporosis guidelines [48–51], so far, there is presently no clear recommendation on the implementation of TBS as a sole indication to commence osteoporosis therapy in subject with borderline BMD or fracture risk assessment tool (FRAX®) or in subjects whose BMD is not adequate to stratify fracture risks.

Generally, osteoporotic treatment is usually initiated for those with osteoporosis as per their BMD scores or those with a high risk of fragility fractures determined by FRAX or have history of fragility fractures [49–52]. However, it is evident that degraded bone microarchitecture,

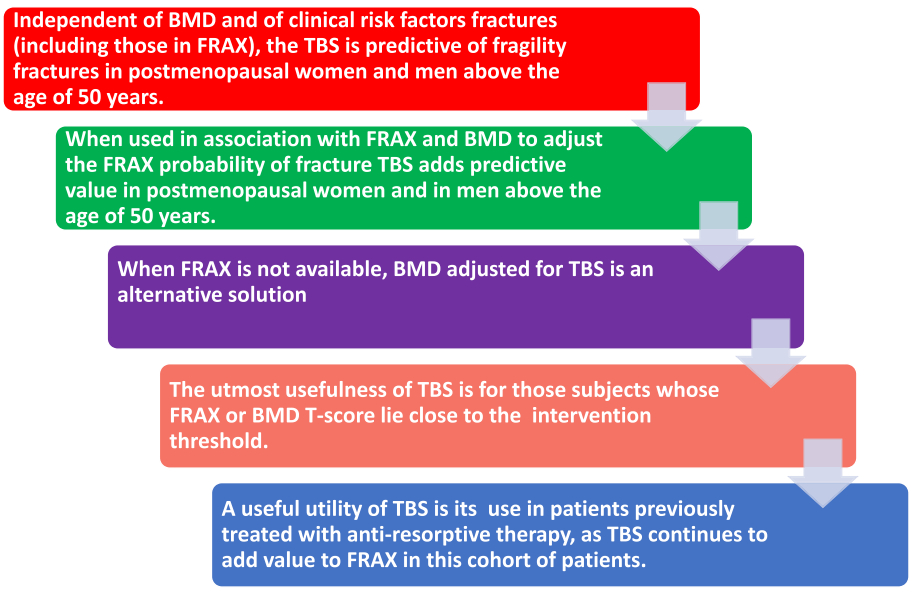


Fig. 3 The value of integrating TBS in clinical practice as a predictive tool for fragility fractures

especially in osteopenic women, may contribute to an increase in fracture risk and therefore cannot be underestimated. Hence, considering anti-osteoporotic treatment in patients with degraded TBS with BMD in the osteopenic range has been suggested by several experts (Fig. 4) [53, 54] (LOE 3.B).

The adjustment of the FRAX for TBS provides a global risk assessment based on both bone microarchitecture as well as bone mass plus clinical risk factors. Alternatively, the adjustment of the lowest BMD for TBS facilitates capturing the fracture risk associated with degraded bone microarchitecture and reduced bone mass. In concordance, the adjusted T score may be included into other fracture risk calculators, such as the Garvan fracture risk calculator [54] (LOE 3.B).

At the conceptual level, TBS may play a role in the decision-making process. The finding that TBS reflects positive changes in the bone microarchitecture has led to the suggestion that TBS is an important confounding factor together with BMD and clinical risk factors to set up specific treatment regimen tailored to the individual patient's needs. Based on this theory, treatment approach might be considered aiming to increase both BMD and bone microarchitecture, with consolidation thereafter as to either increase BMD or preserve bone microarchitecture. However, these suggested strategies require further research to inform such management approaches [55] (LOE 3.C).

Use of TBS for the initiation and monitoring of osteoporosis therapy Although TBS has proven to predict hip and major osteoporotic fracture risk independent of clinical risk factors and BMD [56], there is no evidence to support the use of TBS as a standalone tool to guide the start of treatment. Additionally, it is currently unknown what TBS clinical threshold can be used to initiate anti-osteoporotic therapy [35]. However, evidence has been accumulated on the added utility of TBS for therapy initiation

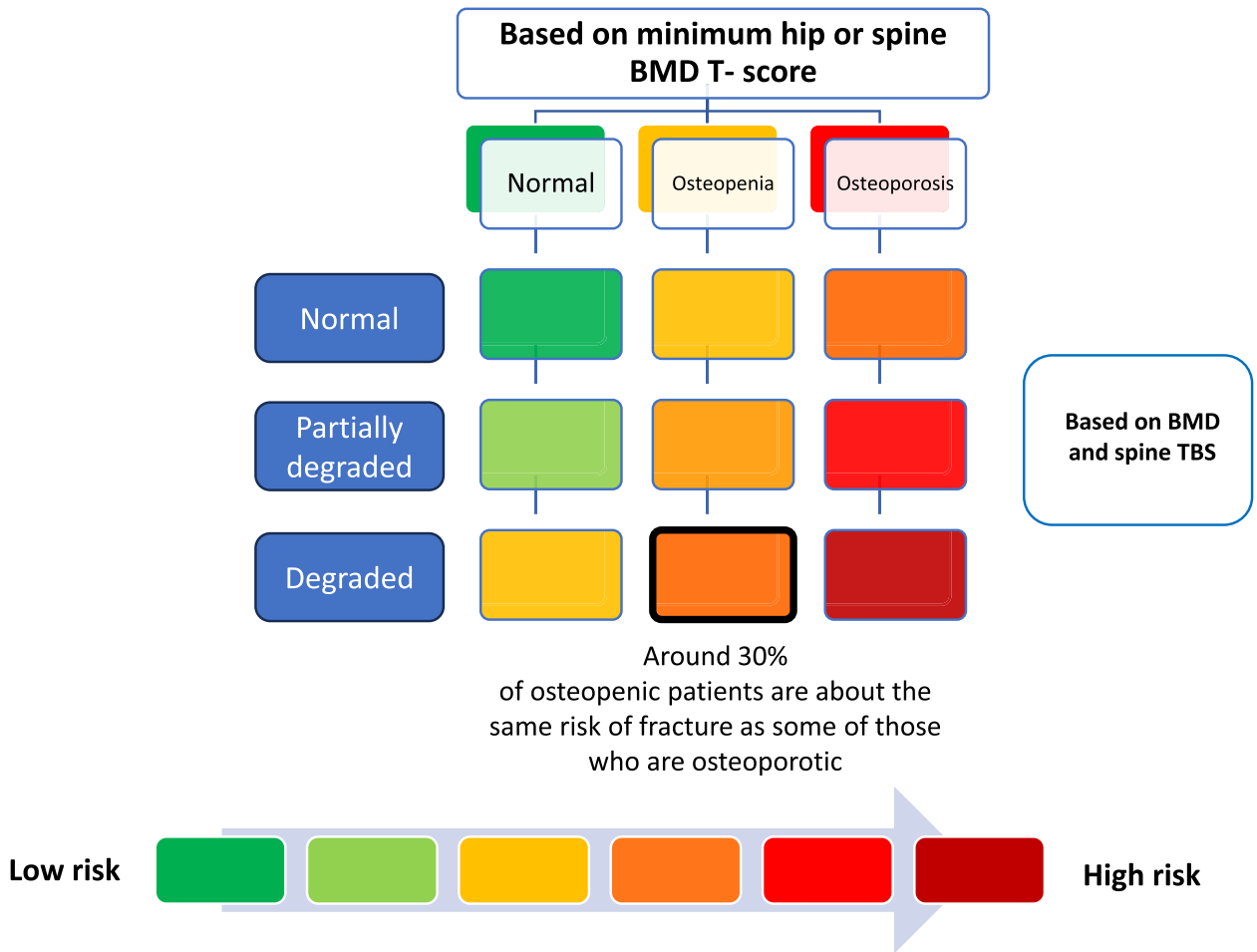


Fig. 4 Clinical implications of combining BMD and TBS for fracture risk prediction and treatment initiation

decisions and understanding the impact of various anti-osteoporotic medications on bone microarchitecture (Fig. 5) [57–62]. Based on that, TBS with BMD and FRAX probability can contribute to stratify the patients according to their fracture risk level and consequently recommend the appropriate osteoporosis therapy based on its mechanism of action. For example, stratifying the patients according to their fracture risk levels would consequently direct the cohort with very high fracture risk to anabolic-first approaches. On the other hand, subjects with low TBS who lie below but near the treatment threshold should be considered for an earlier assessment and lifestyle advice.

The least significant change (LSC) for TBS which is valuable for evaluating the utility of repeated TBS testing for treatment monitoring varied from 3.1 to 5.8% among facilities and was constantly lower than lumbar spine BMD [63]. In most treatment monitoring studies that extend for almost 2 years, the lumbar spine BMD changes were more evident than TBS changes (8.8% for lumbar spine BMD, versus 3.6% for TBS) [64] (LOE 3.C).

The currently available evidence does not support routine TBS monitoring in patients receiving antiresorptive medication [35]. In the studies conducted on oral antiresorptive medications, TBS changes were minimal and not significant (below the TBS LSC) [65, 66]. Moreover, in the Manitoba DXA registry, TBS changes with antiresorptive therapy; mostly bisphosphonate did not predict incident fractures in females aged 40 years and older [57]. Similar findings were

Treatment Initiation	Decision Making	Monitoring
Management: **Patients with low TBS who lie below but near the treatment threshold should be considered for an earlier assessment and lifestyle advice.**	**TBS adds value when:** - **When used with BMD in monitoring skeletal effects of hormone antagonist/ hormone depletion therapy.** - **TBS continues to add value to FRAX in patients previously receiving antiresorptive treatments.**	**-TBS is potentially amenable to change as a result of pharmacological therapy.** **-Evidence supporting the use of TBS in monitoring response to anti-osteoporosis therapy is applicable across both primary and secondary osteoporosis**
Patient Stratification: **TBS with BMD and FRAX probability contributes to the stratification of the patients according to their fracture risk high Vs very high, directing therapy to anti-resorptive Vs anabolic first approach.**	**- used with BMD in monitoring skeletal effects of glucocorticoids.**	**Denosumab:** **TBS in conjunction with BMD, is useful for monitoring individual response to long-term denosumab treatment (5 years or more).**
As TBS captures elements of bone microarchitecture, conceptually, a low (degraded or partially degraded) TBS might support the use of treatments that impact both BMD and bone microarchitecture, for example, long-term denosumab or bone anabolic agents. **Bisphosphonates, SERMs might be considered if the treatment goal is to preserve TBS**	**A decrease in TBS more than LSC during treatment should prompt further clinical review.**	**Anabolics:** **TBS in conjunction with BMD is useful for monitoring individual response to teriparatide, abaloparatide and romosozumab therapy.**

Fig. 5 Use of TBS for treatment initiation, decision-making and monitoring

reported by the HORIZON trial conducted for 3 years in patients receiving 5 mg of zoledronic acid annually, without significant improvement in TBS in over 2/3 of the treated patients [67]. In agreement with the previous findings, the FREEDOM trial did not find significant changes in TBS beyond LSC in the denosumab group compared to the placebo at 36 months, despite a significant increase in lumbar spine BMD among the patients receiving the antiresorptive medication [58]. More investigations are needed to evaluate the probability of significant TBS changes beyond LSC over longer treatment periods (LOE 4.D).

The efficacy of teriparatide 20 mcg daily in improving TBS compared to intravenous ibandronate 3 mg/3 months in postmenopausal women has been investigated. The teriparatide group had a significant TBS gain that exceed the LSC in 62% of the patients, compared to the ibandronate group (4.3% versus 0.3%) [68]. Similarly, teriparatide was found to increase the TBS in patients with glucocorticoid-induced osteoporosis in comparison to the alendronate-treated group over 36-month period [69] (LOE 3.B).

Additionally, in a post hoc analysis of phase 2 trials conducted on postmenopausal women, a more robust gain in TBS was evident with abaloparatide 80 µg compared to teriparatide 20-mcg daily group (+4.2% vs.+2.2%) at 24 weeks [70]. These data suggested that the anabolic agents may have more pronounced effect on bone microarchitecture at a relatively short period compared to bisphosphonates. Data on the effect of romosozumab on TBS changes are still lacking and need to be investigated in future research. Figure 6 provide tips for using TBS in diagnosis, fracture risk determination, and monitoring of osteoporosis therapy.

Is there a role for TBS in sequential osteoporosis management approach?

Osteoporosis management often involves a sequential treatment approach to optimize patient outcomes and minimize fracture risks. Possible treatment sequences include the following: (1) an antiresorptive agent followed by an anabolic agent, (2) an anabolic agent followed by an antiresorptive agent, and (3) an antiresorptive agent followed by another antiresorptive agent. Recently, sequential therapy has been as the optimum treatment option for patients at very high fracture risk [71]. Recent

Diagnosis: The lowest adjusted T-score (lumbar spine, total hip or femoral neck) is used for diagnosis.
Fracture Risk: TBS can be used in the assessment of fracture risk using FRAX-adjusted for TBS directly OR indirectly by using the femoral neck BMD T-score-adjusted for TBS, but not both, to avoid over-adjustment for TBS.
FRAX-adjusted for TBS can be used to adjust the probability of MOF or hip fracture, for bone microarchitecture, in men and women aged 40 to 90 years. The adjusted FRAX probabilities can then be compared to local or national intervention thresholds.
For younger patients (age 20-40 years) Other approaches might include BMD Z-score and the risk threshold adjustment (or treatment threshold shift) referring to the lowest BMD T-score adjusted for TBS Z-score.
The selected approach should reflect patient age and country or region-specific guidelines.
Monitoring:
Least significant change (LSC) should be used to interpret treatment effect at the individual level, based on the center-specific precision error.
The average of published TBS precision errors and corresponding LSCs (Hologic and GE systems) are 1.37%CV and 3.79% respectively.
If a patient has a significant reduction (exceeding LSC) in TBS during treatment, consider causes of secondary osteoporosis and if an alternative treatment is required;
If a patient has a significant increase (exceeding LSC) in TBS and/or BMD during treatment while not expected given the given drugs and their associated mechanism of action, check for possible technical inaccuracies.

Fig. 6 Tips for using TBS in diagnosis, fracture risk determination and monitoring

osteoporosis guidelines endorse the use of an anabolic agent as the first therapeutic regimen (e.g., PTH, PTH/PTHrP analogue, or romosozumab) for 1–2 years, followed by an antiresorptive agent (e.g., a bisphosphonate or denosumab) for a further 5–10 years [72]. Studies revealed that TBS gains, after 24 months, were higher in the anabolic first group (2.7% versus 1.8%) and continued to increase for a further 24 months, following the treatment switch to anti-resorptive agent, particularly with denosumab (5.1% versus 3.6%). In the ARCH multicenter trial, romosozumab therapy for 12 months leads to increase of 5.1% in TBS. This increase was maintained to 4.8% with alendronate, for a further 24 months [72]. In contrast, a control group of women treated with only alendronate, and gains in TBS were lower (1.5% at 12 months, 2.5% at 36 months). This approach may also be useful in patients whose very high risk of fracture is driven by reduced bone density and/or degraded bone microarchitecture [73] (LOE 4.C).

What is the role of TBS in fracture risk prediction in secondary osteoporosis?

Secondary osteoporosis may develop either as a drug-induced comorbidity or a consequence of an underlying disease. However, in most scenarios, the picture may not be that sharp, as most of the time secondary osteoporosis occurs as a result of a mix of risk factors and chronic systemic disorders associated with their medical management. In contrast, the well-documented negative impact of such combination on the BMD and studies assessing their impact on bone micro-architecture are far less common. Nonetheless, it is likely that, along with BMD, bone micro-architecture plays an important role. This, for example, provides an explanation for why there is higher risk of sustaining a low trauma fracture in patients taking glucocorticoids that develop before major loss in the BMD can be recorded on DXA scanning (Fig. 7) [50]. This observation has been linked to the changes induced by glucocorticoids on the bone micro-architecture [74]. Changes in the TBS in secondary osteoporosis are summarized in Fig. 8 and can be stratified into two main categories:

I.Drug induced

1. Glucocorticoids

Glucocorticoids are thought to degrade trabecular bone more than cortical bone. Reduced TBS has been demonstrated with glucocorticoid exposure. In a retrospective cross-sectional study, TBS was better able to discriminate for glucocorticoid

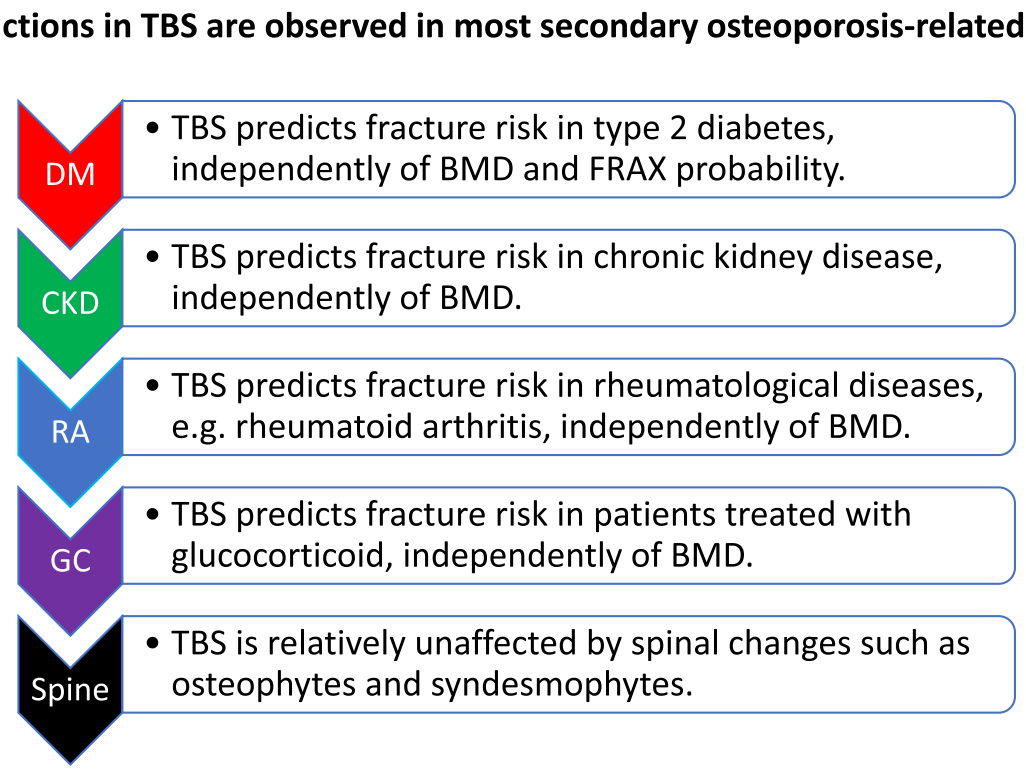


Fig. 7 Use of TBS in the prediction of fracture risk associated with secondary osteoporosis

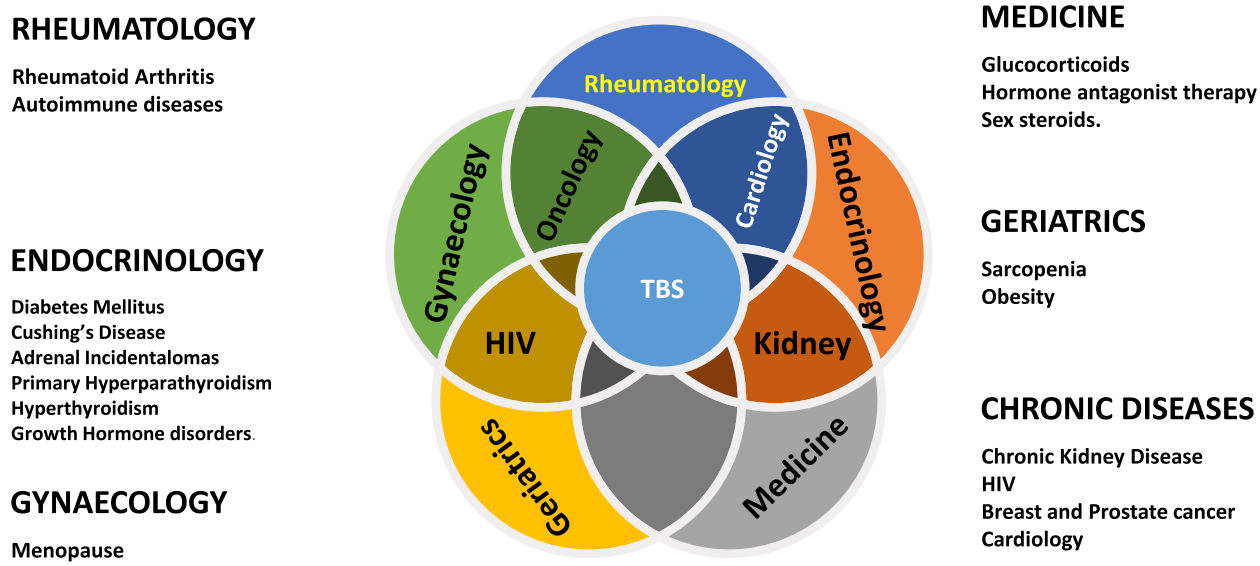


Fig. 8 Secondary osteoporosis impacting on the TBS

use than lumbar spine BMD (LOE 3.B). TBS is generally more sensitive and less specific than osteoporotic range BMD for prevalent fracture, and the combination of both degraded TBS (< 1.230) and osteoporotic range BMD showed high specificity for vertebral fracture and fragility fracture. So, TBS may be particularly useful for fracture prediction in patients exposed to glucocorticoids [75].

2. Aromatase inhibitors
   Aromatase inhibitors (AIs) represent the first-line adjuvant therapy for hormone receptor-positive breast cancer women. AIs have been associated with an increased rate of fractures. TBS appeared to enhance fracture risk prediction in women. It could be speculated that AIs' treatment may differentially affect BMD and TBS within individual patients, thus providing further evidence to the dramatic impact of AIs on bone health [74].
3. Sex steroids
   In adult males, both levels of gender-related steroids and bone mass appear to decrease gradually with age. However, the link between the age-related decline in BMD and the role of androgens in men remains controversial. In the study carried out by Mascarenhas et al. [74] to assess the relationship between both lumbar spine and femoral neck BMD/TBS and the testosterone levels, in 80 healthy adult men (mean age 54 years), results revealed weak but significant correlations between TBS at the lumbar spine and both serum total testosterone as well as the free androgen index. In concordance, in females, both female hormones and total testosterone levels play a role in determining bone quality in terms of TBS [76] (LOE 3.B).

II. Systemic diseases

- TBS in obesity

The triad of osteoporosis, obesity, and fragility fractures represents a major public health problem which require to be contextualized and properly addressed with views towards a prevention plan [77–79]. High amount of soft tissues was reported to be associated with high noise in DXA image with a consequent impact on the DXA-based measurements. Kim et al. [78] concluded that while elevated BMI is linked with high bone density, low BMI is associated with low BMD. In the meantime, TBS decreases with increasing soft tissue thickness. This comes in contrast to TBS measures which were noted to be lower with increasing BMI [78, 80]. Furthermore, earlier data revealed that TBS is negatively correlated with BMI, weight, waist circumference, and total body fat mass. This negative relationship between BMI and TBS was reported in both women and men [79]. Such difference was attributed to the association between increased BMI and insulin resist-

ance. Elevated body weight induces rising insulin resistance. While insulin resistance is not significantly linked to BMD, it is negatively correlated to bone strength (impact strength, bending strength, compression strength) [81].

The changes in the BMI may cause variations in the image pixels causing difficulty in identifying the microstructure bone changes, resulting in underestimation of TBS. To cope with the artefactual decrease in the TBS measures, unrelated to biological variations, a correction has been implemented in TBS based on patient BMI. However, in general, TBS software has not been recommended in individuals with BMI lower than 15 kg/m^2 or greater than 37 kg/m^2 [76]. The recent TBS software (TBSv4.0) seems to overcome the residual negative correlation of the current TBS with body size and composition parameters and to therefore postulate itself as free from this previously acknowledged technical limitation [77] (LOE 3.C)

- Utility of TBS in patients with diabetes mellitus (DM)

  A paradoxical relationship was suggested in type-2 diabetic patients between BMD and fracture risk. This raised the notion that DM may be linked to a decrease in bone strength that is not evident from BMD measurements alone. This was based on the finding of increased risk of bone fragility reported in type 2 DM patients whose BMD was even higher than nondiabetic control individuals [82]. This has been attributed to several factors, such as altered material properties (as a result of the accumulation of advanced glycosylation end products in the organic bone matrix or protein glycation) or impaired bone quality (linked to increased cortical porosity and heterogeneity of trabecular bone microarchitecture). Furthermore, TBS was reported to be negatively correlated with HbA1c levels, fasting insulin levels, and fasting glucose implying impaired bone quality [83, 84]. Also, prediabetics had significantly lower TBS. Overall, in patients with type-2 DM, the adjustment of BMD for TBS incrementally improves fracture prediction [79]. In concordance, a cross-sectional study in which 119 type-1 DM (59 males, 60 premenopausal females; mean age 43.4 ± 8.9 years) and 68 healthy controls were analyzed suggested that TBS values were significantly lower in type-1 DM with prevalent fractures [85] (LOE 3.C).
- Chronic kidney disease

  Reduced kidney function has been defined by KDIGO as glomerular filtration rate (GFR) < 60 ml/min per 1.73 m2 and normal kidney function as GFR ≥ 60 ml/min per 1.73 m2 [86]. In the Canadian Multicenter Osteoporosis Study, Naylor et al. studied the TBS association with fracture risk in patients with impaired kidney function in comparison to subjects with normal kidney functions [87]. Low TBS measures were significantly associated with reduced kidney functions, with a significantly higher probability of fracture. TBS was reported to predict fracture independently of age, sex, FRAX score, BMD, and chronic risk factors. These results suggest that as in the general population, in patients with reduced kidney function, TBS may be a useful parameter to predict the patients' fracture risk.

  Hemodialysis represent another challenge in the bone health standard clinical stetting. In comparison to the general population, fractures are more frequently reported in hemodialysis patients [88]. Furthermore, the mortality risk in association with hip fractures is two times higher in patients with an eGFR < 45 than those with eGFR ≥ 45 ml/min per 1.73 m2 (11, 34, 35). Impaired bone microarchitecture as measured by TBS was reported in the end-stage renal disease patients on dialysis [89]. Even in chronic kidney disease patients on dialysis, TBS was significantly lower among patients without osteoporosis than controls without osteoporosis, and this was independent of BMD, age, body mass index, gender, and chronic risk factors. Therefore, TBS can be a noninvasive and effective indirect marker of bone micro-architecture [90].

  For patients with severe end-stage renal failure, kidney transplantation has the best prognosis [91]. Studies investigating the association of fracture risk with renal transplant revealed contradictory results. Risk factors, such as duration of prior renal failure or dialysis, associated comorbidities such as diabetes mellitus, or medications such as glucocorticoids have been linked, but not strongly, with the increase in fracture risk after renal transplantation. Nevertheless, the subject lacks a well-established research to predict fracture risk in these patients. Naylor and colleagues [2 (below)] investigated TBS in 327 kidney transplant adult recipients. There was a significantly lower TBS among the recipients who sustained a fracture in comparison to those who did not. TBS was able to discriminate significantly (area under the curve 0.64, $p = 0.012$) between recipients with and without a fracture. In addition, the kidney transplant recipients with a lower TBS were less likely

to remain fracture-free ($p = 0.017$). Furthermore, lower TBS was associated with fracture independent of FRAX (LOE 3.B).

- Inflammatory rheumatic diseases
  Patients with rheumatic diseases are at high risk of low bone mass and osteoporotic fractures. The risk factors for the skeletal fragility in these inflammatory rheumatic diseases include the inflammatory status and high rates of bone resorption induced by cytokine activation, in addition to the use of medication known to impact negatively on the bone health and microarchitecture such as glucocorticoid and other immunosuppressive drugs [92]. All studies revealed that TBS was significantly associated with fracture, independent of BMD. Adjustment of BMD as well as FRAX for TBS improved fracture risk prediction [93, 94].
  Considering specific rheumatic diseases, TBS has been consistently lower in patients with autoimmune diseases as rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic sclerosis, systemic lupus erythematosus, and polymyalgia rheumatica and has been associated with disease activity and fragility fracture. TBS was shown to be a FRAX-independent predictor of fracture in incident fracture in AS patients [95] (LOE 3.B)
- Impact of degenerative spine disease on TBS
  It is well-documented that degenerative changes impact on the BMD measurements, typically leading to a falsely increased BMD with a consequent falsely high T and Z scores [96, 97]. Therefore, it has been recommended that when vertebral degenerative changes are present and result in > 1 unit increase in T score of the affected in comparison to the adjacent vertebrae, this specific vertebra should be excluded from the BMD measurement [98]. Previous research revealed that in contrast to the BMD, spine TBS showed no difference between those vertebrae with and without lumbar osteoarthritis (grade 2 or higher). In concordance, TBS score was not correlated with Kellgren-Lawrence grade [99] (LOE 4.C).
- TBS in hyperthyroidism
  Thyroid hormones regulate bone metabolism by influencing the rate of bone turnover or bone remodeling [100]. Bone resorption is accelerated by thyroid hormone, which has been attributed to increased osteoclastic bone resorption, not compensated by osteoblastic bone formation. Interestingly, thyroid hormones are known to preferentially affect the remodeling of cortical than that of trabecular bone [101]. Active Grave's disease been known to be a major risk factor for secondary osteoporosis, as untreated thyrotoxicosis can negatively influence bone health by increasing the rate of bone remodeling. Increased fracture risk and bone loss have been linked to hyperthyroidism [102]. One bone characteristic which assists with the management for those with this thyroid disease is TBS. While there was no difference in BMD between the patients and control groups, there is an obvious correlation between Grave's disease and decreased TBS [103]. Serum T4 levels were found to be associated with the bone microarchitecture changes [104] (LOE 3.C).
- Effect of hyperparathyroidism on TBS
  Elevated parathyroid hormone levels along with hypercalcemia are the hallmarks of primary hyperparathyroidism (PHPT). PHPT often leads to bone loss, even in its asymptomatic presentations; consequently, fracture risk is higher in PHPT patients. In PHPT patients, TBS has been demonstrated to be a predictor of fracture independent of BMD. Moreover, TBS was found to be lower in fractured individuals with PHPT than in non-fractured patients. Additionally, following parathyroidectomy, the TBS values were reported to get improved dramatically [105] (LOE 3.C).

TBS and growth hormone (GH) disorders The anabolic effects of GH are important to achieve peak bone mass and to attain appropriate trabecular bone microarchitecture during late adolescence and early adulthood which affects fracture risk later in life. GH deficiency is related to reduced bone strength, whereas the GH long-term replacement therapy can successfully revert this condition. TBS plays an important role to monitor the effect of GH therapy [106].

In contrast, in acromegaly, patients are predisposed to develop fractures regardless of their BMD values. TBS better defines risk of fracture because BMD is normal or even increased in this cohort of patients. Despite these findings, TBS should not be used alone, but a comprehensive consideration of all fracture risk factors, BMD, and bone turnover markers is necessary [107] (LOE 3.C).

What are the pros and cons of TBS?

Although TBS has been studied for several years, and the fact that it does help to draw a more complete picture of the bone health, it is still not universally used in standard clinical practice or covered by insurance in some countries. In standard practice, machines should be calibrated in the same way as done DXA testing. This gives confidence in the TBS measures provided

and facilitates their comparison. Below is a summary of the pros and cons of TBS.

Pros and advantages are as follows:

- TBS enhances fracture risk prediction in both primary and secondary osteoporosis and across diverse races and ethnicities.
- Together with FRAX, the inclusion of TBS in conjunction with BMD can provide an improved global assessment of fracture risk, which considers the two pillars of fracture resistance (bone mass and bone microarchitecture) and chronic risk factors.
- Where FRAX is not available, TBS alongside BMD provides a dual skeletal assessment of fracture risk, and the lowest BMD T-score adjusted for TBS can be input into other fracture risk assessment tools.
- Limited data suggest that TBS is less influenced by degenerative and inflammatory spinal disease than DXA BMD.
- TBS has the potential to help inform treatment initiation and the choice of treatment in light of the overall skeletal profile of an individual patient, taking into account both BMD and bone microarchitecture.
- Including TBS in the monitoring of treatment may be useful for denosumab and anabolic agents.

Cons and pitfalls are as follows:

- The TBS measures trabecular bone and microarchitecture at the lumbar spine level and was not developed for other skeletal sites. However, hip fracture is the most prevalent type of fractures.
- TBS software have not recommended in individuals with BMI lower than 15 kg/m2 or greater than 37 kg/m2 due to the effects of soft tissue on its results.
- The TBS is measured at the lumbar spine level, a region commonly affected by osteoarthritis and, more importantly, by vascular calcification; this might alter accuracy of TBS.
- There are some other putative factors like image noise or water content of soft tissue that could limit TBS use.

Ongoing and future research TBS is an emerging technology, and future work will add to the existing data, confirming and extending its clinical utility. With the new developments of TBS software, degraded TBS is expected to play an important role in reclassification of the patients and the decision-making to treat osteopenic women, men, and subjects living with secondary causes of osteoporosis [108]. The utility of TBS in children has been limited by the absence of appropriate reference values. This topic has been of interest [109], and more publication are on the way to ensure the implementation of TBS in standard pediatric bone health management. TBS is expected also to play a role in the assessment of the bone microarchitecture quality in the relation to the recent causes of osteoporosis such as bariatric surgery and sleeve gastrectomy. There are some encouraging studies for the use of TBS to assess the bone microarchitecture in other skeletal regions such as the hip [110], lateral vertebral fracture assessment [111], and the distal femur following knee arthroplasty [112].

Discussion

TBS has been recently introduced as an analytical tool that is able to capture bone microarchitecture and is calculated by dedicated software using the gray-level differences in the lumbar spine DXA images. Consequently, TBS helps in determining the individual's fracture risk. TBS offers a 3D evaluation of the bone microarchitecture; as it assesses and goes beyond basic BMD measurement. TBS also evaluate the trabecular number, trabecular separation, and density of connectivity. Therefore, high TBS measures reflect robust bone microarchitecture which is resistant to fracture and vice versa [10, 113, 114]. The strong correlation of the TBS to recognized tools that provide similar information, such as microcomputed tomography of the vertebrae, has been well documented [115].

Several large studies have reported the ability of TBS to measure the strength of the bones and predict the risk of fracture independent of the traditional spine and hip BMD [113]. Though a modest correlation was reported between TBS and BMD, yet both were equally predictive of fractures. When both parameters were used together, the validity of fracture predictions was even stronger. This suggests at least a complementary, though significant, role of TBS in the setting of fracture risk evaluation and prevention [10, 114]. Hence, this article was developed to simplify the interpretation of TBS values in standard practice by stratifying patients according to their risks including both bone quantity and quality as well as fracture risk [115, 116].

TBS has also shown an improving trend with the decision-making of anti-osteoporotic medical management; however, the LSC is high. This means that it can take more than 2 years for the change to manifest. Recently, TBS has been suggested as a tool for monitoring the anabolic osteoporosis therapy. TBS has also been suggested for the assessment of bone strength in patients with secondary osteoporosis. With the currently available data, though TBS can predict fracture risk independently in both genders, it is not recommended as a standalone tool for decision regarding

osteoporosis management. Yet, TBS can be implemented as a tool to complement BMD in the evaluation of bone health [116].

Implementing TBS in standard clinical practice has its limitations. Additional studies are still needed to assess its utility in clinical practice. Future studies should focus on prospectively, adequately powered studies with clinical and radiological fracture endpoints. In addition, further independent studies are warranted in multiethnic populations and in men. Also, clinical studies should be towards gray zones and contradictory states as the effect of soft tissue, osteoarthritis on TBS accuracy. Furthermore, more research is needed regarding the recent versions of TBS and their role in lowering the TBS limitations. Regarding autoimmune disorders, future research should focus on longitudinal studies of TBS as a predictor of incident fracture, with special attention to the impact of glucocorticoid exposure.

In conclusion, this systematic review provided evidence regarding the value of adding TBS in the evaluation and treatment of osteoporosis in clinical practice. The TBS does not directly reflect the bone microarchitecture. Instead, it reflects variations in the gray tones of the DXA image. However, TBS correlates significantly to several measures of trabecular microarchitecture such as trabecular number, spacing, connectivity, and density providing an indirect evaluation of the bone structure quality. Data revealed the positive role of TBS in the prediction of fracture risk both in primary and secondary osteoporosis. Adjustment of FRAX for TBS as well as the enclosure of TBS in conjunction with BMD facilitates the development of an improved global prediction of fracture risk, which takes into account the two pillars of fracture resistance, namely bone mass and bone microarchitecture, in addition to chronic risk factors.

Abbreviations

AS	Ankylosing spondylitis
BMD	Bone mineral density
BMI	Body mass index
CEG	Clinical evidence-based guidelines
CEBM	Centre for Evidence-Based Medicine
CT	Computed tomography
DM	Diabetes mellitus
DXA	Dual x-ray absorptiometry
FRAX	Fracture assessment tool
GH	Growth hormone
GFR	Glomerular filtration rate
HR-pQCT	High-resolution peripheral quantitative computed tomography
LSC	Least significant change
MOF	Major osteoporotic fractures
MRI	Magnetic resonance imaging
PHPT	Primary hyperparathyroidism
RCTs	Randomized controlled trials
TBS	Trabecular bone score
VFA	Vertebral fracture assessment

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Consent for publication
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Competing interests
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